SEX DIFFERENCES IN CEREBRAL VOLUMES OF 8-YEAR-OLDS BORN PRETERM

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We investigate sex-associated effects of preterm birth on cerebral gray matter (GM) and white matter (WM) volumes. Preterm children (n = 65) and 31 healthy, term control children had usable magnetic resonance imaging (MRI) data acquired at 8 years of age. Both GM and WM volumes were significantly reduced in the preterm group compared with controls. However, only males with preterm birth had significantly reduced WM compared with term males (P = .021), whereas WM volumes were equivalent in the female groups. Lower birth weight was associated with reduced WM in both boys and girls with preterm birth, whereas intraventricular hemorrhage (IVH) was associated with reduced GM in girls only. Positive correlations between GM and cognitive outcome were observed in girls with preterm birth but not boys. We conclude that preterm birth has a significant impact on brain development with increased risk for smaller GM and WM cerebral volumes. Males appear particularly vulnerable to adverse effects of preterm birth on WM development. However, girls with preterm birth show stronger correlations between neuro-anatomical variables and both neonatal risk factors and cognitive outcome, compared with boys. These findings indicate that the sex of the very preterm newborn influences the mechanisms by which the developing brain is affected. ***(J Pediatr 2004;145:242-9)***

Approximately 30% to 50% of very-low-birth-weight (VLBW) preterm infants have neurodevelopmental handicaps during their preschool years; 50% require special help in grade school, and 10% will be diagnosed with cerebral palsy.[1-3] Almost 20% of all VLBW preterm infants will have repeated at least one grade in school by 8 years of age.[4,5] Although some preterm children may show improvement in cognitive functioning over time,[6] many continue to demonstrate functional deficits, even into early adulthood.[7-9] The specific mechanisms by which the developing brain is adversely affected by preterm birth are not well understood.[10,11]

The neurological, cognitive, and behavioral handicaps experienced by preterm infants suggest that premature birth disrupts one or more components of cerebral neurodevelopment. In support of this hypothesis, results from magnetic resonance imaging (MRI) studies demonstrated that reduced cerebral volume occurs in newborns, children, and adolescents who have experienced preterm birth, compared with developmental age matched healthy controls.[12,13] MRI studies of preterm infants assessed at term and compared with healthy term infants further suggest particular deleterious effects of premature birth on white matter (WM) volume and structure.[11,14] Males appear to be particularly vulnerable to preterm birth, demonstrating excess morbidity and mortality compared with females.[15,16] Preterm males additionally demonstrate increased neurodevelopmental-cognitive deficits compared with preterm females, including greater impairment in speech, language, academic achievement, and social functioning.[7,17,18]

ANCOVA	Analyses of covariance	TBV	Total brain volume
CSF	Cerebrospinal fluid	VIQ	Verbal IQ
FSIQ	Full-Scale IQ	VLBW	Very-low-birth-weight
GM	Gray matter	WISC-R	Wechsler Intelligence Scale for Children-Revised
IVH	Intraventricular hemorrhage	WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
MRI	Magnetic resonance imaging		
PIQ	Performance IQ	WM	White matter

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However, these sex differences are, as yet, unexplained, as they may occur irrespective of perinatal risk factors and demographic variables.[7,17,18]

Despite the increasing number and sophistication of imaging studies focusing on the effects of preterm birth on brain development, the relative long-term influence of prematurity on cerebral gray matter (GM) and WM remains poorly understood. To test the hypothesis that preterm birth would influence both GM and WM components of the developing brain, we performed volumetric MRI studies on 134 preterm children at 8 years of age, and on 70 prospectively collected age- and sex-matched control subjects. In an attempt to explain the phenomenon of increased morbidity and deleterious neurodevelopmental outcome in males as compared with females with preterm birth, analyses also focused on possible sex-specific influences on neuroanatomy.

METHODS

Subjects

All subjects were recruited and evaluated at the Yale University School of Medicine, New Haven, Connecticut, and at Brown University School of Medicine, Providence, Rhode Island. The institutional review boards of both universities approved the procedures. All children and their parents provided informed written consent for the study. The MRI scans were performed at Yale University School of Medicine and were analyzed at the Stanford Psychiatry Neuroimaging Laboratory.

The preterm subjects consisted of children enrolled in the follow-up portion of the Randomized Indomethacin IVH (intraventricular hemorrhage) Prevention Trial, based on geographic proximity to New Haven, Connecticut. Overall, 287 of the surviving 340 children (84%) were evaluated at 8 years of age corrected age (ie, age from the obstetric due date). Two hundred of these 284 study children (70%) resided within geographic proximity to New Haven and did not have contraindications for MRI (usually orthodontia); all were invited to participate in the imaging study. From this pool of 200 eligible preterm subjects, 134 scans were obtained (67%). As described in the next section, 65 of these scans were deemed usable for quantitative analysis; 34 of these 65 subjects with usable scans (22 males, 12 females) received indomethacin.

In conjunction with the preterm subjects, 70 term control children, 7 to 11 years of age, were prospectively recruited as part of the randomized indomethacin trial from randomly selected names on a telemarketing list of 5000 families in the same geographic region and from local advertisements. The families were identified as having children of the appropriate age and living in the same ZIP code areas as the preterm children.[12] All controls were selected from the indomethacin trial to provide similar distributions of age, sex, and minority status (ie, caregiver report of white or nonwhite) in the two groups.[19] Preliminary data from a total of 19 preterm subjects included in this study have been previously analyzed.[12]

Neonatal Assessment

As previously described,[20,21] neonates of 600- to 1250-g birth weight were recruited to participate in a multicenter randomized IVH prevention trial. All infants were examined with serial cranial ultrasonography; grading systems for documenting the presence of IVH, periventricular leukomalacia, and ventriculomegaly are described elsewhere.[22] Pre-, peri- and postnatal data were obtained prospectively by maternal interviews and from chart review, and all infants underwent gestational age assessment on the first postnatal day. Cognitive and family assessments were performed by research staff blinded to the child's study group and medical status as previously described.[6]

MRI Protocol, Image Processing, and Measurement

MRIs of each subject's brain were acquired with a single GE-Signa 1.5 T scanner (General Electric, Milwaukee, Wis). Sagittal brain images were acquired with a three-dimensional volumetric radio frequency spoiled gradient echo pulse sequence using the following scan parameters: repetition time = 24 msec, echo time = 5 msec, flip angle = 45°, number of excitations = 1, matrix size = 256 × 192 voxels, field of view = 30 cm, slice thickness = 1.2 mm, 124 contiguous slices. The reconstructed images were automatically reformatted to have isotropic voxels of 1.2 × 1.2 × 1.2 mm.

The semi-automated image processing procedure was conducted with the program BrainImage version 5.x running on an Apple Macintosh G3 or G4 computer with operating system MacOS 9.2. Data processing steps included removal of nonbrain tissues from the images, correction of equipment-related image artifacts including bias field inhomogeneity, separation (segmentation) of tissue components (GM, WM, and cerebrospinal fluid [CSF]), normalization of image position, and parcellation of the cerebral cortex into lobe and subcortical regions based on a stereotaxic atlas template.[24] This procedure as described and validated in previous reports,[25,26] results in reliable measurements for GM, WM, and CSF total cerebral, lobe, and deep cerebral volumes (Fig 1). Intra-rater reliabilities for volumes described in this study were all ≥.95 as determined by the intraclass correlation coefficient.

Data Analysis

Data were first examined for normality to conform to the assumptions of the parametric statistical analyses employed. Analyses of covariance (ANCOVA) were performed to analyze group differences in GM and WM tissue volumes. Age was used as a standard covariate in the analyses because of the small, yet significant, difference in age between the two groups, and because many neurodevelopmental processes, such as myelination, are quite dynamic throughout childhood.[27] Sex was also a covariate, and analyses included an interaction term for diagnosis and sex combined.

Although a P value of $< .05$ was used to indicate statistical significance, a two-sided P value of .025 (Bonferroni correction) was selected for the primary analyses (group

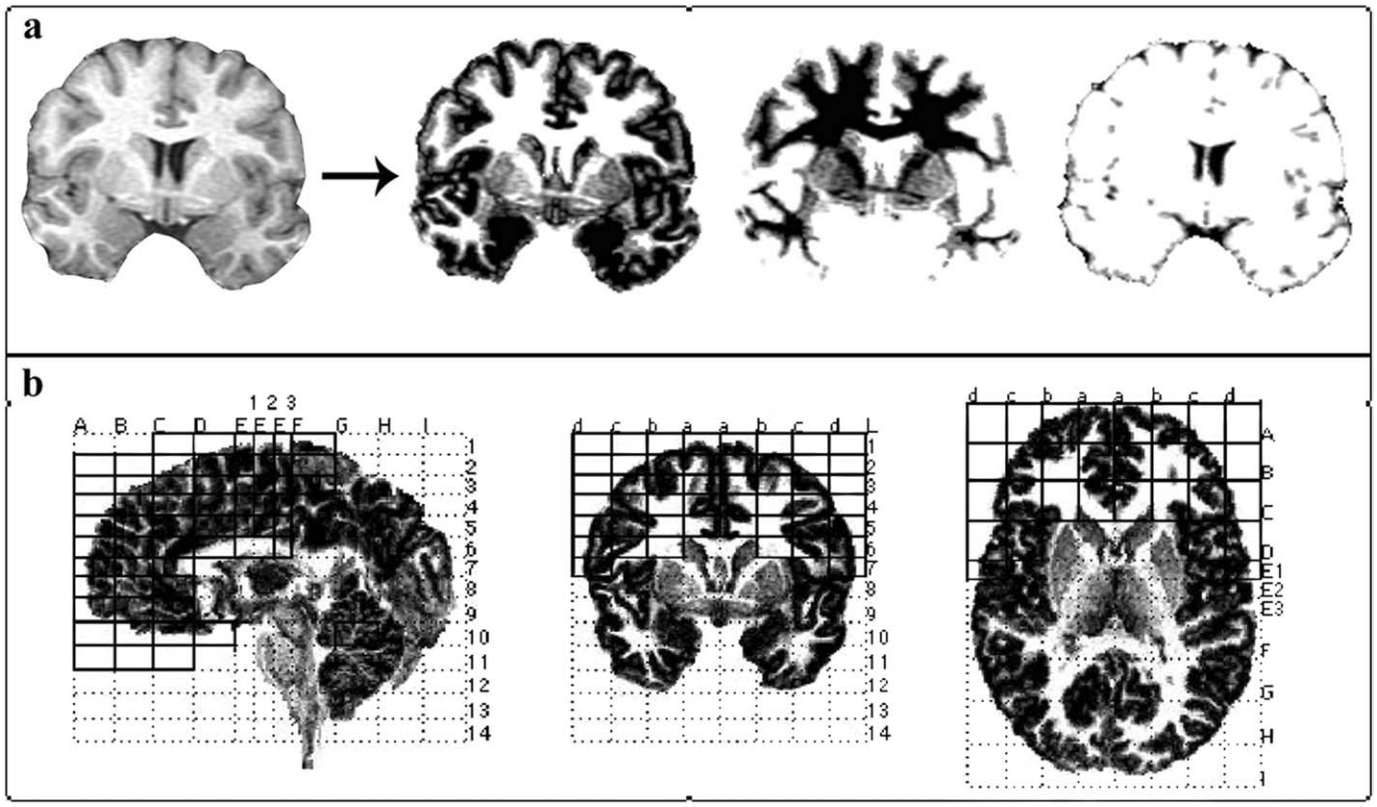

Fig 1. A, Gray scale brain image (left) is separated into GM, WM, and CSF tissues, left to right respectively, using a constrained fuzzy segmentation algorithm. *Voxel* shade represents the proportion of the specific tissue at that location (*darker* = increased). **B**, GM images are shown in multi-planar views in *BrainImage*. The Talairach stereotaxic grid (shown by *dotted and solid lines*) is used for positional normalization and parcellation of brain tissue into subregions. The Talairach sectors corresponding to the frontal lobe are outlined in *solid lines*.

differences in GM and WM volumes) to account for multiple comparisons corresponding to separate GM and WM ANCOVAs. In addition, a more liberal P value of $\leq .10$ was used to decide whether the interaction term of age-by-sex should be included in the model because it is well known that statistical power to detect interactions is lower than for main effects.

Secondary, exploratory analyses used: (1) ANCOVA to further specify the most prominent anatomical locus of group and sex effects on cerebral WM volume and (2) correlational analyses to investigate associations between specific neuroanatomical variables and both cognitive function and selected perinatal variables within the preterm group. A P value of $< .05$ was used for the secondary analyses.

Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill) versions 10 and 11 were used for all analyses, and all P values in this report are of the two-tailed type.

RESULTS

Qualitative Assessment of MRI Data

All scans were pre-screened by research staff blinded to group identity to determine suitability for morphometric analyses. Images containing moderate or greater levels of artifact, such as those related to head movement or blood flow, were excluded from further analyses. The screening procedure uses a lower threshold for exclusion than that typically utilized for qualitative analyses of brain scans to ensure that the quantitative, computer-based analyses are not confounded by poor image quality. This resulted in 68 of the 134 preterm scans (51%) being excluded because of motion and/or vascular flow artifact. One additional preterm subject's scan was excluded because of the presence of a brain tumor detected on qualitative examination, leaving a total of 65 usable scans. Of 70 control scans, 39 (56%) were excluded. These exclusions are consistent with other studies of children of similar ages.[28,29] Statistical comparisons between included and excluded subject groups for both the preterm and term subject groups showed there were no significant differences in terms of sex, maternal education, IQ, or Child Behavior Checklist scores. One preterm subject had ventriculomegaly from examination of the neonatal ultrasonography. None of the subjects had periventricular leukomalacia.

Demographics

On average, children in the preterm group were older (by approximately 7 months) than those in the control group. As expected, the preterm group also had lower mean Full Scale IQ (FSIQ) scores than control children. The two groups were similar in sex and minority status (Table I). The mean birth weight for the 65 preterm subjects was 953 ± 169 g and the mean gestational age was 28.2 ± 1.9 weeks. There were no

Table I. Demographic characteristics; group means and standard deviations or percentages (in parentheses) are shown

	Preterm (n = 66)	Control (n = 31)	*P* value
Males	36 (55%)	14 (45%)	.39
Minority status	31 (47%)	12 (39%)	.45
Age at scan (y)	9.2 (0.7)	8.5 (0.7)	< .0001
FSIQ	93.8 (17.6)	104.4 (15.4)	.005
VIQ	96.2 (18.9)	106.1 (14.5)	.01
PIQ	92.3 (16.4)	101.8 (17.5)	.01

significant differences in perinatal variables for the male and female preterm subjects (Table II). Two preterm females had cerebral palsy.

Cerebral Tissue Volumes

Sex and age at scan were investigated as variables that might moderate the effect of preterm birth on tissue-specific brain volumes (Table III). In comparison with controls, preterm subjects had significantly lower cerebral GM volumes. Both group and sex contributed significantly to the variance in GM volume. Specifically, cerebral GM volumes were significantly reduced in the preterm group compared with controls (P = .003); whereas males (across both groups) had larger cerebral GM volumes than females (P = .002). The interaction between group and sex did not contribute significantly to variation in cerebral GM volume (P = .63), indicating that both males and female preterm subjects had reduced GM volumes compared with same sex controls.

In a comparable fashion, cerebral WM also differed significantly by both group and sex such that WM was significantly reduced in the preterm group compared with controls (P = .006), and in females compared with males (P < .001) (Table III). In addition, this analysis showed a statistically significant group-by-sex interaction (P = .02). Figure 2 displays the finding that boys in the preterm group were observed to have cerebral WM volume reductions compared with boys in the control group. In contrast, girls in the preterm group had cerebral WM volumes that were similar to girls in the control group.

To further elucidate the neuroanatomical regions where the group-by-sex interaction was most significant, secondary analyses were performed for each of the cerebral WM regional volumes (ie, frontal, parietal, temporal, occipital, and deep cerebral WM; see Table III). In comparison with girls, where regional volumes were similar between the preterm and control groups, boys in the control group demonstrated larger volumes than boys in the preterm group across all subdivisions. However, the group-by-sex interaction reached significance for temporal lobe (P = .02) and for deep cerebral WM (P = .002) volumes only (Fig 3). There was a trend seen for a group-by-sex interaction for the frontal and occipital lobes (.05 < P < .10).

Table II. Perinatal variables for preterm subjects; group means and SDs or percentages (in parentheses)

	Male (n = 36)	Female (n = 29)	*P* value
Gestational age (wk)	28.1 (2.0)	28.4 (1.8)	.50
Birth weight (g)	942 (170)	962 (170)	.64
Maternal age (y)	27.4 (5.5)	25.6 (6.3)	.16
Maternal education (y)	13.3 (2.1)	13.3 (2.1)	.96
IVH, any grade, 6-11 h after birth	3 (8%)	5 (17%)	.28
IVH, any grade, 5 d after birth	7 (19%)	6 (21%)	.90
BPD	19 (53%)	12 (41%)	.36
Indomethacin	22 (61%)	12 (41%)	.11
Amnionitis	7 (19%)	3 (10%)	.31

BPD, Bronchopulmonary dysplasia–defined as need for supplemental oxygen and abnormal chest radiograph at 28 days of age.

Association of Neonatal Measures with Neuroanatomical Variables (Preterm Group)

Secondary analyses were performed to examine whether specific neonatal variables predicted neuroanatomical variation within the preterm group. The outcome variable was the ratio of either cerebral WM or cerebral GM volume to total brain volume (TBV). Possible predictors of the outcome variables were specific neonatal measures that demonstrated at least moderate variation in the preterm group and for which there were a priori predictions: birth weight, intervention with indomethacin, and presence of (any) IVH at 6 hours or 5 days. A nonparametric test (Spearman's ρ) was used for these analyses as the data were not normally distributed.

Birth weight was a significant predictor of both the WM/TBV and GM/TBV ratios such that greater birth weight was associated with greater WM and lesser GM proportions in the preterm group (n = 65, WM/TBV: ρ = .33, P = .007; GM/TBV: ρ = −.35, P = .004). Further, although occurring in the same direction for both sexes comprising the preterm group, these correlations tended to be more robust for females (n = 29, WM/TBV: ρ = .55, GM/TBV: ρ = −.49) than males (n = 36, WM/TBV: ρ = .24, GM/TBV: ρ = −.31).

The presence of IVH (any grade) at 6 hours or 5 days did not predict either of the tissue ratios in the overall preterm group. However, IVH at 5 days was significantly (negatively) correlated with reduced GM in preterm girls (n = 29, ρ = −.42, P = .024) but not boys (n = 36, ρ = .04, P = .8). Treatment with indomethacin was not significantly correlated with either of the tissue ratios, either for the preterm group as a whole or when subjects were divided into male and female subgroups.

Association of Neuroanatomical Variables with Cognitive Performance Measures

Secondary analyses also were performed to determine whether the GM or WM proportions would predict cognitive outcome in the preterm group (Table IV). Primary cognitive

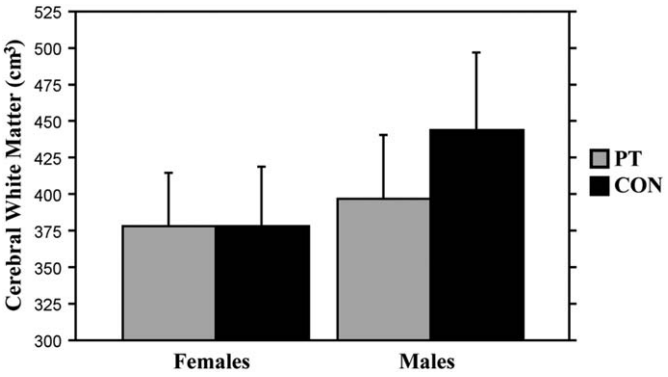

Fig 2. Mean (and SD) of cerebral WM volumes (in cm^3) by group and sex. A significant reduction is observed in males within the preterm (PT) group as compared with control (CON) males. The two female groups show comparable means.

outcome variables consisted of the Wechsler Intelligence Scale for Children-3rd Edition (WISC-III), FSIQ, Performance IQ (PIQ), and Verbal IQ (VIQ) scores at 8 years of age. Because previous work from our group has shown that chronological age and intervention can moderate the effects of preterm birth on cognitive performance,[6] we also analyzed the association between the tissue ratios and FSIQ, PIQ, and VIQ scores collected from preterm subjects when they were 4.5 years of age. These previous scores were obtained with the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) and were available from 62 (VIQ, FSIQ) or 63 (PIQ) of the 65 preterm subjects with usable MRI data.

A significant correlation was observed between the GM/TBV ratio and PIQ at 4.5 years of age(n = 63, ρ = .25, P = .046) such that greater GM proportion was associated with higher IQ. Correlations for the GM/TBV ratio with VIQ at 4.5 years of age (n = 62, ρ = .22, P = .086) and at 8 years of age (n = 65, ρ = .208, P = .097), and FSIQ at 4.5 years of age (n = 62, ρ = .246, P = .054), approached significance. A sex-specific analysis of these significant or near significant neuroanatomical-cognitive associations showed that they were nearly completely explained by positive correlations between GM/TBV ratios and cognitive measures in female preterm subjects tested at both 4.5 and 8 years of age (Table IV). Males in the preterm group failed to demonstrate any significant correlations between neuroanatomy and cognitive outcome at any age group.

DISCUSSION

With continuing improvements in medical technology and, correspondingly, survival of the smallest preterm neonates, increasing numbers of children at risk for neurodevelopmental disability are entering our healthcare and educational systems. These children are vulnerable to neurological dysfunction and disorders of development, cognition, and behavior. The results of this study support the hypothesis that preterm birth adversely affects brain development. Specifically, our findings expand on the results obtained from 25 subjects from this overall preterm cohort[2]

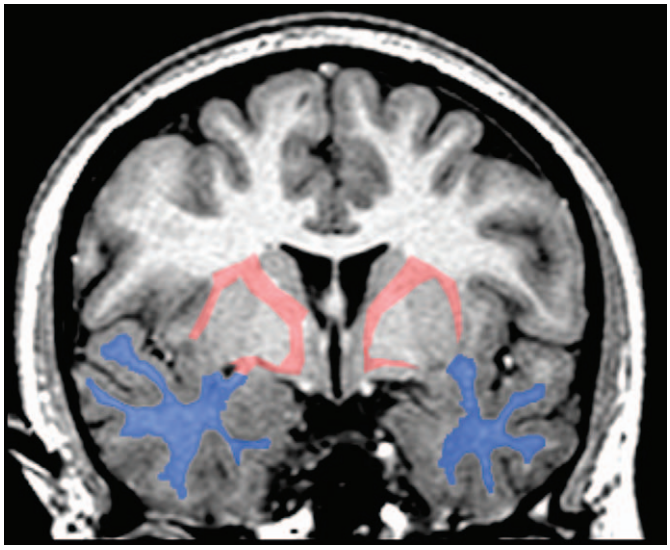

Fig 3. The representative (MRI) image illustrates where WM volumes were significantly reduced in boys born preterm compared with age-matched healthy control males (*blue* = temporal lobe; *red* = deep cerebral region). Preterm girls did not show comparable reductions in WM volume compared with age-matched healthy control females.

(19 overlapping with the present study) by demonstrating that both GM and WM volumes are significantly reduced relative to controls. Further, we observe that WM volume reduction in the preterm group occurs only in boys, whereas preterm girls have WM volumes comparable to girls in the control group. Neonatal risk factors were significantly correlated with both GM and WM proportions, although the results indicated stronger correlations in girls than boys. Similarly, GM proportion was strongly correlated with cognitive outcome at both 4.5 and 8 years of age in preterm girls, with relatively little evidence of a similar relationship in boys.

Using nonquantitative methods, numerous imaging studies of preterm children have shown that recognizable cerebral insults such as parenchymal brain injury and observable abnormalities of myelination are correlated with suboptimal developmental and cognitive outcome.[30,31] Recently, Nosarti et al performed quantitative assessment of cerebral GM and WM tissue components of preterm subjects with gestational age < 33 weeks and term controls.[13] Findings included a 6% reduction in brain volume accompanied by reduction in cerebral GM but not WM (after statistically adjusting for TBV and sex).

Differences between our findings and those of Nosarti et al could be explained by several factors. First, the tissue segmentation procedure for measurement of GM and WM volumes in the present study utilized a well-validated, semi-automated algorithm[25] in contrast to the lower resolution stereological (point-picking) technique used in the Nosarti study. In addition, the mean age of subjects in our study was approximately 9 years, whereas the Nosarti study evaluated adolescents 14 to 15 years of age. Studies of typically developing children have shown that brain maturation is

Table III. Neuroanatomical variables by group (all values are in cm^3)

	Preterm males (n = 36)	Preterm females (n = 29)	Control males (n = 14)	Control females (n = 17)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Cerebral GM[**b]	654.6 (49.7)	627.6 (46.6)	694.3 (68.6)	648.0 (54.1)
Cerebral WM[**c†]	396.7 (44.3)	380.8 (33.5)	443.7 (52.7)	378.1 (40.2)
Frontal lobe WM[c]	142.6 (16.5)	135.7 (12.0)	157.2 (22.9)	134.9 (18.1)
Parietal lobe WM[*b]	107.7 (12.5)	104.8 (11.6)	117.2 (12.9)	105.4 (11.6)
Temporal lobe WM[**c†]	62.2 (9.3)	59.1 (7.0)	72.8 (14.0)	58.8 (6.5)
Occipital lobe WM[c]	47.5 (8.3)	45.1 (7.9)	53.4 (10.1)	42.5 (7.4)
Subcortical WM[*a†]	36.7 (3.7)	36.2 (3.4)	43.1 (5.1)	36.5 (4.7)
Cerebral CSF	99.3 (14.4)	104.7 (18.2)	110.7 (17.3)	109.5 (16.0)

Significant group effect (control > preterm; $^*P \leq .05$, $^{**}P \leq .01$).
Significant sex effect (males > females; $^aP \leq .05$, $^bP \leq .01$, $^cP \leq .001$).
†Significant group by sex interaction (preterm males < control males *and* preterm females = control females; $P \leq .05$).

Table IV. Spearman correlations (ρ) between the GM or WM to brain volume ratios with cognitive outcome measures in the preterm group at 4.5 and 8 years of age

	GM/Brain volume			WM/Brain volume		
	All	Male	Female	All	Male	Female
WPPSI-R, administered at 4.5 y						
FSIQ	.246‖	.096	.548‡	−.167	−.065	−.299
FSIQ	.220‖	.170	.364‖	−.210	−.149	−.309
PIQ	.253*	.016	.614§	−.128	−.025	−.213
WISC-III, administered at 8 y						
FSIQ	.195	.007	.477†	−.127	−.007	−.248
VIQ	.208‖	.100	.375*	−.178	−.154	−.199
PIQ	.117	−.058	.430*	−.076	.069	−.232

Numbers of subjects are as follows: WPPSI-R (4.5 y)—62 total: 34 males, 28 females; WISC-R (8 y)—65 total: 36 males, 29 females.
* < .05; † < .01; ‡ < .005; § < .001; ‖ < .10.

associated with both increasing WM and decreasing GM volumes within the age range encompassing both study populations.[27,32] The trajectory of volume changes during middle childhood and adolescence may be dissimilar for GM and WM. Specifically, the trajectory of WM expansion is more linear[33] and relatively greater[34] than the corresponding negative trajectory of GM reduction. Further, the magnitude of WM development appears relatively greater in boys compared with girls.[32] Accordingly, sex-specific differences in myelination, glial proliferation, or axonal growth in boys with preterm birth between the ages of 9 (our population) and 14 to 15 years (the Nosarti population) may explain, in part, the GM-WM differences between the studies. Longitudinal imaging studies should help to clarify this issue.

Although sex effects on WM were observed throughout the cerebrum, the temporal lobes and deep cerebral (peristriatal) regions were particularly affected in the preterm group (Fig 3). WM tracts within these areas play important roles in a variety of behaviors including sensorimotor function, attention, emotion, reading, and language.[35,36] Complementary imaging techniques for analyzing WM structure, such as diffusion tensor imaging and voxel-based morphometry,[37,38] should be used to further explore this finding.

The fact that boys with VLBW have greater neurodevelopmental morbidity than girls is not unexpected in the general context of the epidemiology of neurodevelopmental disorders in children.[15,16] Compared with girls, boys are significantly more prone to have a wide variety of these disorders including mental retardation, attention deficit hyperactivity disorder, learning disabilities, and autism.[39] To compliment the neuropsychological findings of others, our data now suggest differences in brain structure in preterm males compared with females.

We observed that birth weight, a commonly acknowledged correlate of clinical morbidity and mortality associated with preterm birth,[40] was positively correlated with cerebral WM and GM proportions. Birth weight and gestational age are highly correlated, and Nosarti et al noted a significant correlation between WM volume and gestational age in their preterm group.[13] Inder and colleagues examined MRI in VLBW preterm subjects studied at term and noted that WM injury was already directly correlated with gestational age.[11]

IVH also was correlated with neuroanatomy in our preterm group but only in girls. Similarly, neuroanatomical variation was more strongly correlated with IQ in preterm girls compared with boys. Male-female differences in correlations between neuroanatomical variables and both neonatal risk factors and IQ support the premise that neurobiological factors affecting brain development and cognitive outcome in preterm children may differ on the basis of sex. This finding may have implications for sex specific strategies for prevention of, and recovery from, neurodevelopmental adversity associated with preterm birth.

One limitation to the generalizability of this study was the slightly lower prevalence of adverse neonatal factors in the 65 preterm subjects with usable MRI data compared with other preterm cohorts. For example, only one of these 65 subjects had ventriculomegaly, and none had periventricular leukomalacia, compared with rates of 5% and 4%, respectively, in the entire cohort of 371 subjects. The fact that significant differences in neuroanatomy occurred in our preterm group despite a relatively lower rate of identifiable central nervous system risk factors underscores the potential for deleterious neurodevelopmental consequences of preterm birth beyond those associated with identifiable brain anomalies.

Both the structure-function relationship and the cellular and molecular underpinnings of these findings remain to be explored. Nonetheless, our data support previous suggestions that one or more processes underlying WM development,[10,38] such as myelination, axonal growth, and glial proliferation, may be particularly affected by premature birth, that this effect may be most severe for those infants with the lowest birth weights, and that the developing brain may be particularly vulnerable to WM injury in preterm males.

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